INTERNATIONAL JOURNAL OF PHARMACEUTICAL RESEARCH AND BIOMEDICAL ANALYSIS | ISSN: 2278 –2664
| JUL-SEPT 2014| VOLUME 3 | ISSUE 3| 11-21
Available Online Through: www.ijprba.com

Research Article

DEVELOPMENT AND *IN-VITRO* EVALUATION OF DELAYED RELEASE TABLETS OF RABEPRAZOLE SODIUM

G Sridhar Babu*[1], D Vijay Kumar[1], Ch Jyothi[1], P S Malathy[1], H Ramana[2]

[1]Pragathi Pharmacy College, Pemberthy, Jangaon, Warangal Dist, Telangana-506201 India

[2] Mohammadiya Institute of Pharmacy, Arempula, Khammam Dist, Telangana-507163 India

***Corresponding author E-mail: sridharppcj@gmail.com**

ABSTRACT

The main objective of this research work was to formulate and evaluate the Delayed release tablets of Rabeprazole sodium, an anti ulcer drug like peptic ulcer and duodenal ulcer. Rabeprazole was class-I Proton pump inhibitor to gain FDA approval. Rabeprazole sodium Delayed release tablets were prepared by Direct Compression method using different excipients as well as with varying concentration of polymer proportions using HPMC Phthalate 55 (HPMCP 55) as enteric coating material. All the excipients are tested for compatibility with drug, which revealed that there was no physical and chemical interaction occurred. During compression tablet appearance, average weight, hardness, thickness, friability, disintegration time was evaluated and enteric coated tablets were evaluated for Hardness, thickness and In-vitro drug release studies. From the results F8 fulfilled all the specifications of the physical properties and invitro release and is comparable to the innovator product.

KEY WORDS

Rabeprazole sodium, Delayed release tablets, HPMC Phthalate 55, In-vitro drug release.

INTRODUCTION

Oral route is the most preferred route of administration for most of the drugs due to various advantages. For most drugs, conventional drug delivery is effective, but some drugs which posses narrow therapeutic window and which cause irritation to gastric mucosa require modified drug delivery system to achieve desired therapeutic effect. These delivery systems have a number of advantages over traditional systems such as improved efficiency, reduced toxicity and improved patient convenience [1].

Enteric coated or delayed release tablets are solid unit dosage forms meant for oral administration and are designed to bypass the stomach and release the drug in small intestine. Such preparations contain an alkaline core material comprising the active substance, a separating layer and enteric coating layer. Rabeprazole sodium drug is a sodium salt of 2-((4-(3-methoxypropoxy)-3-methylpyridin-2-yl) methylsulfinyl)-1*H*-

benzo[d]imidazole belongs to a class of proton pump inhibitors (PPIs). It suppress gastric acid secretion by specifically inhibiting the H+/K+- ATPase enzyme system at the secretory surface of the gastric parietal cell [2]. Rabeprazole sodium is very soluble in water and in alkaline media. The stability of Rabeprazole sodium is a function of pH; it is rapidly degraded in acid media, and is more stable under alkaline conditions. The degradation is catalyzed by acidic reacting compounds and PPIs are usually stabilized in mixtures with alkaline reacting compounds. Therefore exposure of Rabeprazole sodium to the acidic content of the stomach would lead to significant degradation of the drug and hence, reduced bioavailability. Rabeprazole sodium delayed release tablets are prepared by direct compression and coated using polymers like HPMC Phthalate 55 to delay the release. All enteric coated tablets are delayed release tablet but all delayed release tablet are not enteric coated tablets [3].

The aim of present work was to prepare Delayed release i.e., enteric coated tablets of Rabeprazole sodium by using HPMC Phthalate 55 as Enteric coating polymer in perforated coating pan to prevent degradation in the stomach due to the acidic environment or gastric enzymes and to treat duodenal ulcers.

MATERIALS & METHODS

Materials

Rabeprazole sodium was obtained as gift sample from Hetero drugs, Mannitol, Crospovidone, Sodium carbonate anhydrous, Sodium Stearyl Fumarate, Ethyl cellulose, HPMCP 55, Myvacet were obtained as gift sample from apex pharmaceutical, Chennai. All other ingredients used were of analytical grade.

Methods

Preparation of Rabeprazole delayed release tablets:

Core Tablets

Rabeprazole sodium delayed release core tablets were prepared by direct compression technique using different excipients shown in Table 2. Rabeprazole Sodium, Sodium Carbonate anhydrous, Mannitol, and Crospovidone passed through sieve # 30 and mix for 30 mins. Sodium Stearyl Fumarate sifted and added to the prepared blend. The powder blend was lubricated with magnesium stearate and talc. Compress the lubricated blend into tablets [4].

Enteric Coating

Disperse Ethyl cellulose in dehydrated ethanol under stirring to prepare clear solution add Water insoluble polymer and stir well. Divide the core tablets into 2 equal lots and coat tablets in a coating machine with ethyl cellulose dispersion to achieve a target weight gain of 4.0 ± 0.5% w/w and 6.0 ± 0.5% w/w each. Warm the Seal-coated tablets in coating pan at 50°C ± 5°C for 20-30 mins. Disperse HPMC phthalate (HPMCP-55) in mixture of dehydrated ethanol and purified water (80:20) under stirring to prepare clear solution. Add diacetylated monoglycerides to

the prepared solution. Prepare dispersion of pigment blend yellow with purified water using homogenizer and add to the above solution and stir well. Coat the seal coated tablets (4%w/w and 6%w/w) in a coating machine with coating solution to achieve a target weight gain of 10.0 ± 0.5% w/w. Warm the enteric-coated tablets in coating pan at 50°C ± 5°C for 20 -30 mins [5].

PREFORMULATION STUDIES

Drug excipients compatibility study

Drug Excipients compatibility studies were carried out by mixing the drug with various excipients in different proportions. Studies were carried out in flint vials at Accelerated conditions, 40ºC ± 2°C / 75% RH ± 5 % RH. The studies were conducted for 4 weeks and compared with control at 2-8°C. Physical observations of the blend were recorded at regular interval of two weeks.

Pre Compression Parameters

Angle of repose

Angle of repose has been used as indirect methods of quantifying powder flow ability, because of their relationship with inter particle cohesion. A static heap will slide when the angle of inclination is large enough to overcome frictional forces and stop when gravitational forces balance the forces. The sides of heap will make an angle with horizontal which is called angle of repose.

Angle of repose $\theta = \tan^{-1} h/r$

Where h is height of pile and r is radius of pile.

Bulk density

Bulk density is given by the mass "m" of the powder occupying a known volume 'v' according to the relationship and expressed in gm/cc.

P_b = (M/V)

It depends on particle size, shape, tendency of particle to adhere.

Tapped density

Weighed powder sample was transferred to a graduated cylinder and was placed on tapped density apparatus, was operated for a fixed number of taps (100). It is the ratio of weight of sample to tapped volume.

Tapped density = mass/tapped volume

Carr's Index

Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug was determined by using the following formula [6].

%Compressibility= tapped density-bulk density/tapped density X100

Hausner's Ratio

The ratio of tapped density to bulk density of the powders is called the Hausner's ratio.

Hausner's Ratio = Tapped Density / Bulk density

Post Compression Parameters

Weight variation:

All prepared matrix tablets were evaluated for weight variation. In this twenty tablets of each batch were used to evaluate weight variation among tablets and standard deviation was calculated.

Friability:

Friability testing was done by Friability test apparatus (Lab India Friability Apparatus FT 1020). The percentage friability was then calculated by,

% Friability = $[(W_1 - W_2) / W_1] \times 100$

% Friability of tablets less than 1% is considered acceptable.

Hardness:

Hardness of all batches was determined using Tablet hardness tester (Monsanto hardness tester) [7].

Thickness:

Thickness was measured by vernier calipers and readings were carried out in triplicate and average value was noted.

Disintegration time

The disintegration time of the six tablets were measured by using USP Disintegration apparatus at 37.5 ^{0}C [8].

In vitro dissolution studies

The In Vitro dissolution study of delayed release tablets of Rabeprazole was determined using USP dissolution testing apparatus II (paddle Type). The dissolution test was performed using 900 ml of 6.8 pH Phosphate buffer, at 37 ± 0.5°C and 100 rpm. A sample (10 ml) of the solution was withdrawn from the dissolution apparatus at regular interval for 60 minutes, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45 µ membrane filter and absorbance of these solutions was measured at 284 nm using a Shimadzu UV-1700 UV/Vis double beam spectrophotometer [9]. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

RESULTS & DISCUSSION

Twelve formulations of enteric coated tablets of Rabeprazole were developed by preparing core tablets using mannitol as diluent and Crospovidone as super disintegrant and sodium carbonate as Stabilizer in different proportions and varying the compositions of sub coating and enteric coating using Pigment yellow, Myvacet and HPMC Phthalate. The core tablets were prepared by direct compression method.

Pre formulation studies

From the results of Micromeritic studies of the Rabeprazole sodium it was concluded that Rabeprazole sodium has poor flow property and compressibility property (Table 5). From the physical observation, no significant Drug-Excipient interaction was notified. So it was concluded that drug and other excipients were compatible with each other shown in Table 6.

Evaluation of powder blend

From the Micromeritic studies of powder blends of different batches prepared by direct compression and angle of repose of all formulations were found in the range of 25.55 to 29.51. The compressibility index falls in the range of 14.54 to 17.71 % and Hausner's ratio values were in the range of 1.2 to 1.6. It was

concluded that prepared blends showed good flow properties shown in Table 7.

Evaluation of core tablets

The data obtained for post compression parameters of prepared Rabeprazole sodium core tablets such as weight variation, friability, hardness, thickness and disintegration time are shown in Table 8. The hardness of prepared core tablets was in the range of 7.1 to 7.8 kg/cm^2 which was in acceptable range of delayed release formulation. The thickness of all the formulated tablets was in range of 3.94 to 4.0 mm due to the constant tablet press setting across all the batches irrespective of weight variation. The average weight of tablets was found to be uniform in the range of 134.5 to 137 mg and the percent deviation in weight variation for all the formulated layer was within the acceptable range of pharmacopoeial specification. The percent friability value for all formulated layer was in range 0.18 to 0.57% indicated good handling properties of prepared tablets. The *in vitro* disintegration time for core tablets was found to be 94 to 174 sec (Table 8).

Evaluation of Coated Tablets

Rabeprazole delayed release tablets were prepared by enteric coating of core tablets and found to have biconvex surface, circular shape having 7.0 mm diameter. The physical properties such as hardness, friability, thickness, and weight and % drug content of prepared delayed release tablets were presented in. The hardness of tablets was range from 8.4 to 9.6 kg/cm^2. It was also observed that the variation of thickness was minimal. The thickness of prepared tablet ranged from 4.04 to 4.10 mm; also it was observed that increasing polymer concentration resulted in slight decrease in thickness of the tablet formulation. This result might be due to binding property of polymer (Table 9).

In vitro dissolution studies of Formulated tablets were conducted in 900 ml of 6.8 pH phosphate buffer using USP dissolution testing apparatus II. All the tablets were resistant to acidic pH and do not show any drug release. Among all the formulations, F8 shows 98% drug release in 60 minutes and results were shown in Table 10 & Figure 1. Optimized formulation (F8) of Rabeprazole delayed release tablets was compared with Marketed product (PARIET 20mg) and the results suggested similar drug profile (Table 11 & Figure 2).

Table: 1 Pharmacopoeial specification for Carr's index

% Carr's Index	Properties
5-15	Excellent
12-18	Good
18-21	Fair
23-35	Poor
33-38	Very poor
>40	Very very poor

Table: 2 Formulation of Rabeprazole Core Tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Rabeprazole sodium	20	20	20	20	20	20	20	20	20	20	20	20
Mannitol	87.1	77.1	67.1	57.1	47.1	37.1	84.6	74.6	64.6	54.6	44.6	34.6
Na_2CO_3 Anhydrous	10	10	10	10	10	10	10	10	10	10	10	10
Crospovidone	10	20	30	40	50	60	10	20	30	40	50	60
Hydroxy Propyl Cellulose	2.5	2.5	2.5	2.5	2.5	2.5	5	5	5	5	5	5
Sodium starch Fumarate	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7
Talc	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35
Magnesium Stearate	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35	1.35

Table: 3 Composition of Seal Coating stage

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ethyl cellulose	1.62	2.16	2.7	4.05	2.7	4.05	2.7	4.05	2.7	4.05	2.7	4.05
Water insoluble polymer (compound A)	-	-	2.7	4.05	2.7	4.05	2.7	4.05	2.7	4.05	2.7	4.05
Ethanol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table: 4 Composition of Enteric Coating Stage

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
HPMCP 55	17.17	17.50	16.85	17.17	16.85	17.17	16.85	17.17	16.85	17.17	16.85	17.17
Myvacet	1.72	1.75	1.69	1.72	1.69	1.72	1.69	1.72	1.69	1.72	1.69	1.72
Pigment blend Yellow	2.58	2.62	2.52	2.58	2.52	2.58	2.52	2.58	2.52	2.58	2.52	2.58
Ethanol	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Purified water	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s

Table: 5 Micromeritic properties of API

Sample	Angle of Repose (⁰)	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index (%)	Hausner's Ratio
API	34	0.5214	0.7684	32.14	1.473

Table: 6 Drug excipients Compatibility Study

S.No	Name of the Excipient	API: Excp Ratio	Initial Observation	Final observation	
				40°C/75% RH	
				2nd week	4th week
1	API (Rabeprazole sodium)	---	White to yellowish white	White to yellowish white	White to yellowish white
2	API+ Stabilizer (Compound A)	1 :0.5	White fine powder	White fine powder	White fine powder
3	API + HPC	1 : 1	off-white	Off-white	Off-white
4	API + Water insoluble polymer	1 : 1	white	White	White
5	API + Mannitol SD-200	1 : 1	Off white	Off white	Off white
6	API + Sodium Stearyl Fumarate	1 : 0.05	White	White	White
7	API + Mg. Stearate	1 : 0.05	White	White	White
8	API + Ethyl cellulose	1 : 2	White	White	White
9	API + Crospovidone	1: 1	White	White	White
1	API + HPMCP-55	1:1	White	White	White
11	API + Pigment blend (yellow)	1: 0.5	yellow	yellow	yellow
12	API + Myvacet	1:0.5	White	White	White

Table: 7 Micromeritic properties of powder blends of different batches

Formulations	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's Index (%)	Hausner's ratio	Angle of repose(°)
F1	0.710	0.834	17.71	1.17	28.38
F2	0.696	0.873	16.76	1.25	27.36
F3	0.483	0.681	17.03	1.40	25.55
F4	0.467	0.672	16.88	1.43	29.11
F5	0.461	0.714	14.54	1.54	27.72
F6	0.447	0.719	15.77	1.60	28.14
F7	0.500	0.600	15.33	1.20	28.39
F8	0.487	0.613	16.98	1.25	26.31
F9	0.541	0.691	14.66	1.27	25.48
F10	0.526	0.687	17.29	1.30	28.47
F11	0.501	0.605	17.19	1.20	27.23
F12	0.517	0.646	16.19	1.24	29.51

Table: 8 Evaluation parameters of Uncoated Tablets of Rabeprazole sodium

Formulation	Hardness Kg/cm^3	Thickness (mm)	Friability (%)	Weight Variation (mg)	Disintegration time (sec)
F1	7.8	3.97	0.45	135.2±0.01	170
F2	7.4	3.99	0.52	136±0.03	157
F3	7.2	3.97	0.21	137±0.03	110
F4	7.4	3.99	0.18	136±0.02	104
F5	7.1	3.97	0.38	135.8±0.03	107
F6	6.8	3.95	0.57	136.4±0.03	98
F7	7.4	3.99	0.46	134.5±0.05	170
F8	7.8	3.94	0.48	135.6±0.04	106
F9	7.5	4.00	0.55	136.8±0.05	113
F10	7.8	3.98	0.49	134.7±0.05	117
F11	8.0	3.92	0.42	137.9±0.04	94
F12	7.6	3.94	0.48	135.7±0.05	96

Table: 9 Evaluation parameters of Rabeprazole sodium Enteric coated Tablets

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Hardness (kg/cm^3)	8.6	8.4	8.6	8.8	8.7	8.5	9.0	9.4	9.2	9.6	9.6	9.4
Thickness (mm)	4.05	4.07	4.04	4.08	4.05	4.04	4.10	4.04	4.06	4.08	4.04	4.05

Table: 10 *In-vitro* Dissolution profile of Rabeprazole sodium delayed release Tablets (F1-F12)

Time (min)	Cumulative % Drug release											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
10	36	43	46	52	56	58	41	54	52	63	67	68
20	46	52	58	68	76	78	54	59	64	78	82	84
30	56	64	72	75	78	83	69	78	84	89	97	98
45	68	74	85	87	89	93	84	89	98	99	--	--
60	73	79	89	92	93	95	93	98	--	--	--	--

Table: 11 In-vitro dissolution profile of Optimized formulation and Marketed product

Time(min)	F8	PARIET
0	0	0
10	54	56
20	59	61
30	78	76
45	89	87
60	98	97

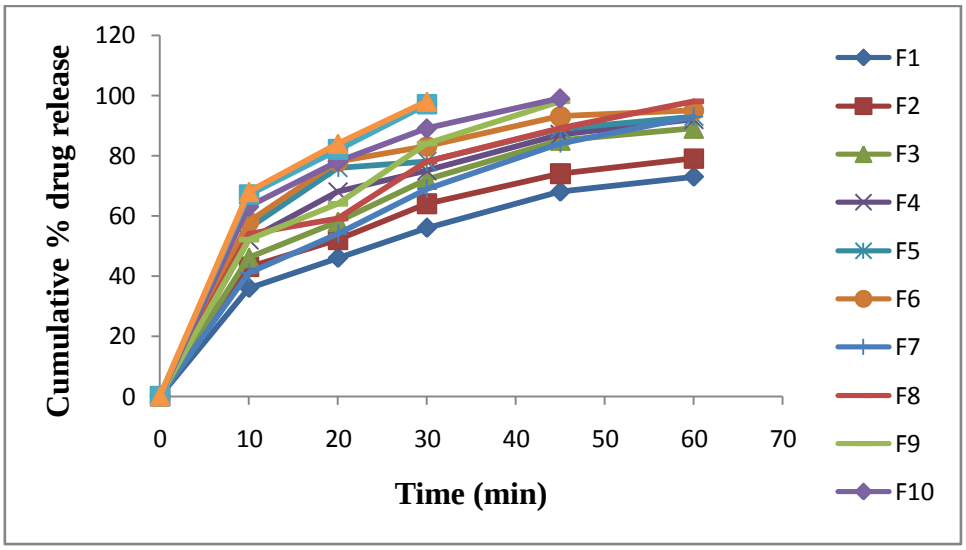

Fig: 1 *In-vitro* dissolution profile of Delayed release tablets (F1-F12)

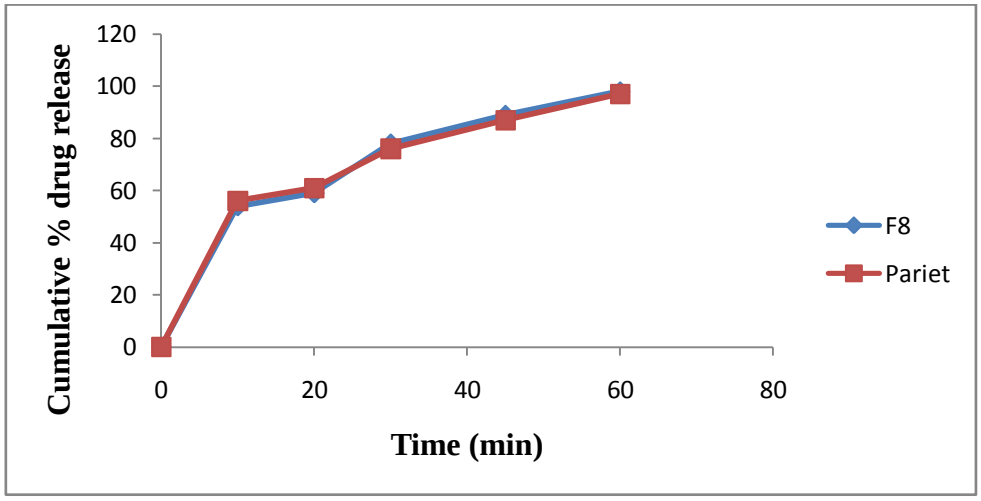

Fig: 2 Comparison of Dissolution profile of Optimized formulation (F8) with marketed product (PARIET)

CONCLUSION

In the present investigation a stable composition of delayed release tablets of Rabeprazole sodium were formulated and evaluated. These results clearly reflect that the prepared formulation offers effective resistance in acidic environment and starts its release in the alkaline environment of small intestine. The final formulation also shows good comparative dissolution profile with marketed preparation.

ACKNOWLEDGEMENT

The authors thankful to the Management of Pragathi Pharmacy College, Jangaon, Warangal, for providing required facilities to carry out this research work.

REFERENCES

1. Lachman L., Lieberman H.A., Kanid J.L. In: The theory and practice of industrial pharmacy. Philadelphia, PA: Lea and Febiger; 1991: 297-298.
2. Tauseef Ali, Roberts DN, Tierney WM: Review- Long-term Safety Concerns with Proton Pump Inhibitors. *The Am J Med* 2009; 122(10):896-903.
3. Aulton ME, Wells TI. Pharmaceutics: The Science of Dosage Form Design. London, England: Churchill Livingston; 1998. p.247.
4. G. Sridhar Babu et al., Formulation and Evaluation of Fast dissolving Tablets of Carbamazepine by Direct Compression using superdisintegrants. *Int. J. Ph.sciences letters,* 2014; 4(5): 432-436.
5. Sanjay R Patel et al., Optimization and evaluation of delayed release tablets of Rabeprazole sodium. *Int J Pharmacy Pharm Sci* 2010; 2(3): 144-156.
6. Brahmankar DM and Jaiswal SB. Biopharmaceutics and Pharmacokinetics; "A Treatise" Vallabh Prakashan, 1995; 1st Ed.: 347-352.
7. Garcia, C. V., Paim, C. S., Steppe, M., Elfrides E.S. Development and validation of a dissolution test for Rabeprazole sodium in coated tablets. *Journal of Pharmaceutical and Biomedical Analysis* 2006; 46: 833–837.
8. Thomson AB., The concept of complete remission of gastro-oesophageal reflux disease: comparative efficacy of pantoprazole and esomeprazole. *Clin Drug Investig,* 2007; 27(10):663-72.
9. G Sridhar Babu et al., Formulation and *In-vitro* Characterization of sustained release Matrix Tablets of Metformin Hydrochloride, *JGTPS* 2014;5(4): 2085-2092.